Retinal degeneration depends on Bmi1 function and reactivation of cell cycle proteins

Dusan Zencak, Karine Schouwey, Danian Chen, Per Ekström, Ellen Tanger, Rod Brenner, Maarten van Lohuizen, and Yvan Arsenijevic

AUTHOR SUMMARY

Retinal dystrophies leading to blindness are a major social and economical burden for healthcare, as well as for affected patients and their families. Retinitis pigmentosa (RP) is a heterogeneous group of genetically inherited diseases that result in the loss of rod and cone photoreceptors. Symptoms of RP include night blindness, narrowing of the visual field, and loss of vision. RP is a major cause of blindness in developed countries, affecting more than 1 million patients or ~1 in 4,000 people. At least 200 different genes and loci are mutated in patients with RP. A full and up-to-date list of these mutations is available on the Retnet Web site (www.sph.uth.tmc.edu/Retnet). The heterogeneity of disease-causing mutations limits the feasibility of efficient pharmacotherapies or gene replacement therapies.

Known cellular mechanisms underlying photoreceptor loss in RP include oxidative stress, intracellular calcium overload, and DNA damage. Interestingly, these mechanisms also underlie a number of neurodegenerative disorders unrelated to the retina, including Parkinson disease (PD), Alzheimer’s disease (AD), and amyotrophic lateral sclerosis (ALS). These diseases also represent a major social burden, as there is a lack of curative or disease-modifying treatments because the underlying causes are complex and unresolved.

Cell cycle regulation is affected during the processes of apoptotic cell death in many neurodegenerative disorders. Under normal conditions, neurons do not divide and are permanently postmitotic. In neurodegenerative diseases, neurons that enter the process of apoptotic death express markers of cells that have attempted to reenter the cell cycle. This seems to be a key event in neuronal apoptosis, and many studies (2) have addressed this question. However, attempts to modulate cell cycle proteins in neurodegenerative diseases have previously shown only modest rescue of the affected neuronal populations. Although the idea that neurons reactivate cell cycle proteins before death arose from retinal tumor studies in the early 1990s (3), the cell cycle hypothesis has never been investigated in the context of retinal degeneration.

In this study, we explored the implications of cell cycle-related proteins in photoreceptor cell death in several animal models of RP-bearing mutations in the rod cGMP-Phosphodiesterase-6b (Pde6b) and Rhodopsin genes. These mutations are relevant to human RP. We found cell cycle protein reexpression in the degenerating photoreceptor cells of all tested models. We then focused on the Rd1 mouse, the most studied genetic mouse model of human RP. This mouse model bore a mutation in the Pde6b gene, similar to that in patients with impaired function of rod photoreceptors, which are important for vision in dim light. In this model, the rod photoreceptors are lost very rapidly whereas cones, which are essential for day and color vision, are functional but die following the loss of rod photoreceptors. A similar pattern of cell death is observed in human patients. Researchers have studied the Rd1 model for decades and applied various neuroprotective agents including antioxidants, calcium blockers, neurotrophic or antiapoptotic factors, and gene therapy. Still, none of these studies achieved more than a modest rescue of the degenerative phenotype. We used several strategies to interfere with cell cycle protein action in photoreceptors in Rd1 mice, with the goal of rescuing or delaying the degeneration of their retinas. We cultivated the...
degenerating retina ex vivo in the presence of drugs that blocked the function of specific proteins implicated in cell cycle progression. Interestingly, we observed an ~40% reduction in cell death during early stages of the degenerative process, showing that these proteins participate in the neurodegenerative process. Most notably, we showed that alterations in a gene called Bmi1, involved in the cell proliferation process, can profoundly influence the degeneration of rod and cone photoreceptors in Rd1 mice. The Bmi1 protein plays a permissive role in cell cycle progression in a number of cell types, including neural stem cells (4, 5). However, its role as a cell cycle regulator has never been investigated in the context of neurodegenerative diseases. We found that deletion of the Bmi1 gene allows an unanticipated survival of photoreceptors in the Rd1 model. Rd1 mice experienced a nearly complete loss of photoreceptors by 30 d of age. However, Rd1 mice carrying a Bmi1 deletion expressed fewer cell cycle proteins and maintained around 60% of the photoreceptors present in healthy animals (Fig. P1), suggesting that inhibition of one gene can enhance the survival of rods. Because these photoreceptors provide essential support to cones, the rescued rods allowed for nearly 75% survival of cones; furthermore, the surviving cones were functional. These experiments show that the course of retinal degeneration can be strongly delayed, ensuring the maintenance of retinal activity.

As described above, there are various causes of RP, but our findings suggest that the reexpression of cell cycle proteins is a common feature in the process of photoreceptor death. Our studies raise the possibility that all RP forms might be influenced via modulation of the Bmi1 molecular pathway and that molecules could be developed to target this pathway for general pharmacotherapy or gene therapy to treat patients with RP. Also, blocking the cell cycle protein-related death mechanisms could extend the therapeutic window for young patients affected by such diseases who are waiting for a curative approach by gene therapy or cell replacement. Because cell cycle activation is involved in the apoptotic death of neurons in a number of diseases, including PD, AD, and ALS, the Bmi1 pathway merits further investigation in other neurodegenerative disorders that affect the brain and spinal cord.